Obesity Corrupts Myelopoiesis

Peter J. Murray[1,*]
[1]Departments of Infectious Diseases and Immunology, St. Jude Children's Research Hospital, Memphis, TN 38105, USA
*Correspondence: peter.murray@stjude.org
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Ongoing monocyte infiltration and subsequent macrophage seeding of adipose tissue is thought to be a key feature of obesity pathophysiology. Nagareddy et al. (2014) show that adipose cells locally activate IL-1β in macrophages in part through the alarmin S100A8/A9, which stimulates bone marrow myelopoiesis to perpetuate nonresolving inflammation.

Obesity is a form of nonresolving inflammation because the insulting entity, excess fat, is not removed from the body. Other forms of nonresolving inflammation include cancer (ongoing growth of malignant tissue), atherosclerosis (cholesterol crystals), neurological pathologies (amyloid and other agents that cannot be removed from the brain), latent and long-lived infections (tuberculosis, leprosy), autoimmune diseases (Crohn's disease, for example), and scenarios in which entities cannot be removed (foreign bodies such as medical devices) or asbestos (Nathan and Ding, 2010). Understanding nonresolving inflammation is critical from a public health perspective, because this type of inflammation is linked to the major diseases afflicting modern societies. The nonresolving inflammation of obesity is associated with a maladaptive local immune response characterized by increased numbers of activated macrophages inside adipose tissue. In this issue of *Cell Metabolism*, Nagareddy et al. (2014) define a regulatory loop in which inflamed adipose tissue and the bone marrow (BM) communicate via IL-1β, causing seeding of fat with monocytes.

The biology of nonresolving inflammation centers on the sequence of events after attempts by the immune response to eliminate the inciting entity. Links between local immune responses, hematopoiesis, and nonresolving inflammation have been recognized, especially in cancer where myeloid-derived suppressor cells (MDSCs) are associated with malignancy, originate in the BM, and represent excessive "emergency hematopoiesis" to clear the insult (Gabrilovich et al., 2012). A model for the involvement of BM in nonresolving inflammation includes corrupted hematopoiesis, in which excess myeloid cells are released into the circulation. Increased myeloid output may contribute to unresolved inflammatory responses in each pathology listed above, but vary in their timing and amplitude depending on the underlying disease.

A landmark in understanding obesity was the recognition that "inflamed" macrophages associated with obese but not healthy adipose tissue (Weisberg et al., 2003). Macrophages invading adipose tissue originate from the BM and are thought to perpetuate the local maladaptive inflammatory response. Therefore, a significant question in the field of obesity research, and indeed in nonresolving inflammation in general, concerns the chicken-and-egg scenario linking inflammation and the disease: Is inflammation necessary to perpetuate the pathology, or a product of disease with other ramifications? A related question concerns the timing and extent of therapies to abate inflammation in unresolved disease, and their consequences should the underlying insult remain. So far, these events cannot readily be separated, because modeling or dissecting an inflammatory-linked disease cannot be done in the absence of inflammation.

Nagareddy et al. first showed that genetically obese Ob/Ob mice or mice with diet-induced obesity (DIO) have enhanced production of myeloid precursors in the BM, a reversible process in DIO when animals were returned to a normal diet (Nagareddy et al., 2014). The numbers of committed myeloid progenitors and granulocyte-macrophage progenitors were higher in Ob/Ob mice reconstituted with wild-type BM, indicating the presence of excess fat is a driver of myelopoiesis, rather than the underlying genotype. These data were buttressed by transplanting fat tissue from visceral adipose tissue of lean mice or Ob/Ob mice. Indeed, fat transplantation was an ingenious method used to tease apart several of the key mechanisms involved in the signals sent between adipose tissue and the BM.

Knowing there may be factors made in fat capable of directly or indirectly inducing myelopoiesis, Nagareddy et al. screened for relative increases in different inflammatory factors in visceral fat of obese mice compared to controls from lean mice. The authors centered on the high relative mRNA expression of the cytoplasmic calcium-binding "alarmins" S100A8/A9. Reasoning S100A8/A9 might be a local inflammatory signal provoking inflammation, they tested the effects of loss-of-function mutants on fat-induced myelopoeisis using TLR4, a receptor capable of interacting with S100A8/A9, RAGE (another receptor capable of binding S100 proteins), Myd88, CD14, and the NLRP3 inflammasome. By screening different reciprocal BM and fat transplants, Nagareddy et al. established that fat-derived S100A8/A9 is a local stimulant of macrophage TLR4-Myd88 to increase IL-1β mRNA. The IL-1β precursor is processed by the NLRP3 inflammasome to produce mature IL-1β, which transits to the BM to provoke myelopoiesis. One of the key experiments described was the transplantation of visceral fat from Ob/Ob mice where macrophages were selectively depleted by liposomes loaded with the bisphosphonate toxin, clodronate. Macrophage-depleted fat failed to drive myelopoiesis to the same extent as macrophage-replete fat from lean mice.

While Nagareddy et al. have revealed new details about fat-BM communication, several elements of the pathway require elaboration. First, other hematopoietic

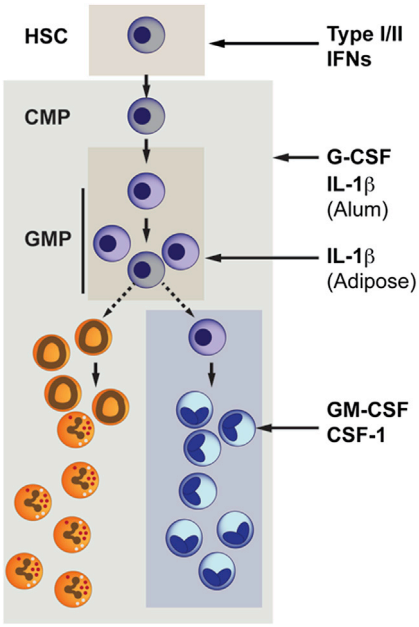

Figure 1. Different Cytokines Have Overlapping and Complementary Effects of Hematopoiesis Depending on the Inflammatory Context

Shown is a highly simplified diagram of the hematopoietic tree along the myeloid lineage where different cytokines propel cell production forward. Nagareddy et al. (2014) show that IL-1β, via the IL-1R, primarily effects CMP/GMP stages, producing monocytes that seed adipose tissue. IL-1R signaling has previously been shown to control neutrophil production in alum-induced inflammation (Ueda et al., 2009). G-CSF has a broad role in overall myelopoiesis, while IFN signaling seems to regulate HSCs.

factors are likely involved in the process, not just IL-1β, as the effects observed on myelopoiesis were relative changes in the amplitude of the response. Contribution from other cytokines could include inflammation-induced G-CSF, CSF-1, and GM-CSF, whose placement into the overall pathway requires definition. The same group recently showed that GM-CSF and CSF-1 are drivers of myelopoiesis in hyperglycemia; S100A8/A9 also stimulates this pathway, but in this case the alarmins originate from neutrophils and signal via RAGE (Nagareddy et al., 2013). A second caveat concerns the final fate of the monocytes, which seed and develop into fat-associated macrophages: since the process is ongoing in nonresolving inflammation, and occurs over time frames of months to years, one possibility is that macrophage death is also a component of the inflammatory process. The elimination of macrophage corpses, themselves likely loaded with other corpses, is a relatively unexplored component of nonresolving inflammation.

Nagareddy et al. clearly place IL-1β as a systemic hormone capable of stimulating myelopoiesis. How does IL-1β fit into the bigger puzzle of long-range inflammatory stimulation of the hematopoiesis (Figure 1)? Other studies have shown IL-1β as a key cytokine to stimulate granulopoiesis in alum-induced inflammation via stimulation of multiple points on the hematopoietic tree, including early stem cells (Ueda et al., 2009), while the type I and type II (IFN-γ) interferons have selective effects on early stem cells, provoking their division in infection to produce more innate inflammatory cells (King and Goodell, 2011). Work from the Link laboratory has shown that G-CSF appears to modulate multiple levels of the hematopoietic tree; although the end product of G-CSF therapy is recorded as increases in circulating neutrophils, the effects of G-CSF on hematopoiesis, and myelopoiesis especially, are broad (Richards et al., 2003). Taken together, different phases of inflammation regulate hematopoiesis differentially, governed by the predominant circulating cytokines, and producing cells according to need (Figure 1). A simple model would be inflammatory cytokine control of blood cell development evolved coincident with infection. However, in nonresolving forms of inflammation, many of which arise later in life (obesity, atherosclerosis, cancer), the production of innate hematopoietic cells from the BM becomes corrupted by circulating cytokines, which would normally be transiently produced. Further investigation of the interaction points between systemic inflammatory cytokines and the hematopoietic system will provide new insights into chronic inflammation.

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